

U.S. Patent Application Serial No. 10/532,682
Amendment filed March 19, 2010
Reply to OA dated October 21, 2009

REMARKS

Claims 1 and 3-9 are pending in this application. Claim 8 is canceled without prejudice or disclaimer, and claim 1 is amended herein. Upon entry of this amendment, claims 1, 3-7 and 9 will be pending. Entry of this amendment and reconsideration of the rejections are respectfully requested.

No new matter has been introduced by this Amendment. Support for the amendment to claim 1 may be found in the specification at page 6, lines 5-16.

Claims 1 and 3-8 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Office action p. 2)

Reconsideration of the rejection is respectfully requested.

Claim 1 recites: "wherein the trace amount of water supplied is within such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent and water." The Examiner states that this phrase and the term "trace amount" are indefinite.

In response, at page 7, lines 1 to 5, of the specification as filed, it is described that the phrase "such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent" is used herein to mean a trace amount of water that can be dissolved in a water-insoluble organic solvent.

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Accordingly "the trace amount of water" means the amount of water that can be dissolved in a water-insoluble organic solvent, and this term is therefore defined.

"The water-insoluble organic solvent" of the present invention is "aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons or a mixture thereof." For any given solvent, it is very easy for a person having an ordinary skill in this field to know the amount of water that can be dissolved in "aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons" by documents or data base.

For example, of IUPAC-NIST Solubility Database, Version 1.0 of NIST Standard Reference Database 106 by National Institute of Standards and Technology (NIST), which is one of the most authoritative data base of properties in the world (available at website <http://srdata.nist.gov/solubility/index.aspx>), discloses the solubility of water in many organic solvents such as aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, etc., and methods of researching thereof.

For the Examiner's reference, Applicant has attached a portion of this Database (seven pages) describing solubility of water in hexane, heptanes or toluene. Those pages describe each amount of water that can be dissolved in hexane, heptanes or toluene of 100 g as follows;

hexane	:	0.025g (313.15K; 40°C)
heptane	:	0.0077g (10°C)
toluene	:	0.0228g (0°C)

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As stated in this database entry, the amount of water that can be dissolved in hexane is 0.025g/100g (i.e. 250ppm). Accordingly, it is clear that the amount of between 1 and 100 ppm in present claim 9 is within such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent and water.

Thus, the the trace amount of water that can be dissolved in water-insoluble organic solvent such as aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons or a mixture thereof, within such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent and water, as recited in claim 1, is a defined term and is readily available to those of skill in the art in documents or databases.

Accordingly, Applicant submits that the recitation of "trace amount" and "such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent" does not render the present claims indefinite.

Claim 7 is rejected under 35 U.S.C. §102(b) as being anticipated by Bills (US 1,775,548).
(Office action p.3)

Claim 7 remains rejected under 35 U.S.C. §102(b) as being anticipated by Knol (US 2,536,753). (Office action p.3)

The rejection of claim 7 is respectfully traversed, and reconsideration is requested.

Bills (US 1,775,548) discloses a process of purifying ergosterol and it describes that the final yield, excluding second crops, amounted to 60 grams by excellently purifying 100 grams of crude

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ergosterol (column 2, lines 85 to 95). That is, Bills discloses that the final yield of ergosterol purified by crystallizing is 60% of crude ergosterol.

On the other hand, Knol (US 2,536,753) discloses a process of recovery and purification of sterols. In Example 4 of column 7, lines 29 to 37, it is described as follows;

"... A mixture of 2g. ergosterol and 20g cetyl-alcohol is dissolved in 100 cm³ iso-octane; 3g of anhydrous ZnCl₂ are added and the mixture is heated for half an hour on a steam bath under continuous stirring. The cooled reaction product is then treated in a centrifuge. By decomposition of the addition product with water 1.95g of a product are obtained containing 92% ergosterol. The yield is 90%...."

That is, it means that the yield= $(1.95 \times 0.92) \div 2 = 0.897 \approx 90\%$.

However the "yield" of Bills or Knol (respectively 60% and 90%) is a completely different parameter from the "crystallinity" in the present claim 7, which means an amount of crystal component in the aggregate by measuring water of hydration by thermogravimetric analysis. The "yield" of Bills or Knol is a parameter corresponding to the "recovery rate" of the present invention (please see page 9, lines 1 to 3, and Examples 1 to 3 of the originally filed English specification).

Applicant has previously discussed the definition of the "crystallinity" parameter on page 4, 3rd paragraph, of the response filed on September 2, 2009.

That is, ergosterol precipitated and separated by controlling the water supply in the method of separating ergosterol of the present invention is an aggregate which does not only comprise generally known hydrate crystals, but also comprises amorphous component as well as hydrate crystals in the crystals thereof (please see page 9, lines 4 to 10 of the originally filed English specification).

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The value of the "crystallinity" parameter in present claim 7 can be obtained by measuring a ratio of hydrate crystals in the aggregate, which does not only comprise generally known hydrate crystals, but also comprises amorphous component as well as hydrate crystals in the crystals thereof, by way of measuring water of hydration by thermogravimetric analysis (please see page 10, lines 9 to 22, of the specification as filed). Accordingly, the "crystallinity" recited in present claim 7 is completely different from the "yield" of Bills or Knol.

In addition, neither Bills nor Knol discloses an aggregate which does not only comprise generally known hydrate crystals, but also comprises amorphous component as well as hydrate crystals in the crystals thereof. Furthermore they do not disclose the amount of crystal component in the aggregate.

Consequently the present claim 7 is not anticipated by Bills or by Knol.

Claims 1, 3, 6 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bills (US 1,842,929), which relies on (US 1,775,548). (Office action p.4)

Reconsideration of the rejection is respectfully requested in view of the amendment to claim 1. Claim 1 has been amended to recite "precipitating ergosterol from said solution containing ergosterol in water-insoluble organic solvent by cooling crystallization."

Bills ('929) discloses a process of preparing ergosterol by processing fungus fat extracted from fungi, by using suitable solvents, of which acetone is one (column 1, lines 37 to 40).

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In the first step of Bills (929), to 100cc. of fungus fat is added 500cc. of acetone, this solution is mixed with a solution of caustic alkali, preferably potassium hydroxide, previously prepared by dissolving 25 grams of the alkali in 200cc. of 95 percent ethyl alcohol, the solution is boiled gently for five to ten minutes to saponify it, and then allowed to be cooled (column 1, line 41 to column 2, line 54).

In the second step of Bills (929), one liter of water is added to the saponification mixture, and the resultant solution chilled to about twenty degrees below zero centigrade so that all of the ergosterol is precipitated as an amorphous mass, then the precipitate is removed from the soapy liquid by filtration or by centrifugal separation (column 2, lines 65 to 78).

That is, a process of Bills (929) comprises steps of extracting fungus fat from fungi by using suitable solvent, of which acetone is one, saponifying the fungus fat in acetone and 95% ethyl alcohol, and precipitating the ergosterol by adding water to the saponification mixture. However, the acetone and ethyl alcohol are not "water-insoluble organic solvent." That is, Bills (929) does not precipitate ergosterol from a water-insoluble organic solvent, and is therefore different from the present invention.

The Examiner states that yeast fat, being fat, comprises aliphatic hydrocarbon.

However, fat is not an organic solvent. In addition, as clear from the fact that Bills (929) saponifies the fat, fat is an ester comprising of alcohol (tri-glycerol) and acid, that is, it is not a hydrocarbon (a chemical compound comprising from carbon atoms and hydrogen atoms).

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On the other hand, all the organic solvent of claim 1 is a hydrocarbon or halogenated hydrocarbon. (Aliphatic hydrocarbons and aromatic hydrocarbons are a chemical compound comprising from carbon atoms and hydrogen atoms, and halogenated hydrocarbons are a chemical compound comprising from carbon atoms, hydrogen atoms and halogen atoms).

As mentioned above, fat is not a hydrocarbon. In addition, the fungus fat of Bills ('929) cannot be a solvent precipitating ergosterol by a cooling crystallization.

Furthermore Bills ('548) purified 100 grams of crude ergosterol prepared in Bills ('929) by employing a mixture consisting of three volumes of acetone and one volume of ethyl ether and obtained the crystals. And the final yield amounted to 60 grams, i.e., the yield from crude ergosterol is 60 percent.

However, as mentioned above, the "yield" parameter in Bills ('548) is not the "crystallinity" parameter of the present invention, which means an amount of crystal component in the aggregate by measuring water of hydration by thermogravimetric analysis.

Thus, neither Bills ('548) nor Bills ('929) discloses the following features of the present invention.

A) To precipitate ergosterol by a cooling crystallization from a water-insoluble organic solvent.

B) To supply a trace amount of water to water-insoluble organic solvent wherein the trace amount of water supplied is within such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent and water.

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C) The ergosterol is separated by precipitation as an aggregate having a crystallinity of 50% to 90%.

Claims 1, 3, 6 and 7 are therefore not obvious over Bills (US 1,842,929) and (US 1,775,548), taken separately or in combination.

Claim 5 is rejected under 35 U.S.C. §103(a) as being unpatentable over Bills (*supra*) as applied to claims 1, 3, 6 and 7 above, in view of Nimberger et al., (US 5,498,138). (Office action p.5)

Reconsideration of the rejection is respectfully requested in view of the amendment to claim 1.

As discussed in regard to the above rejection over the Bills references, Bills ('929) discloses a process of preparing ergosterol by processing fungus fat extracted from fungi, by using suitable solvents, of which acetone is one (column 1, lines 37 to 40).

In the first step of Bills ('929), to 100cc. of fungus fat is added 500cc. of acetone, this solution is then mixed with a solution of caustic alkali, preferably potassium hydroxide, previously prepared by dissolving 25 grams of the alkali in 200cc. of 95 percent ethyl alcohol, the solution is then boiled gently for five to ten minutes to saponify it, and then allowed to be cooled (column 1, line 41 to column 2, line 54).

In the second step of Bills ('929), one liter of water is added to the saponification mixture, and the resultant solution chilled to about twenty degrees below zero centigrade so that all the

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ergosterol is precipitated as an amorphous mass, then the precipitate is removed from the soapy liquid by filtration or by centrifugal separation (column 2, lines 65 to 78).

In Bills ('929), 500cc. of acetone and 200cc. of 95 percent ethyl alcohol are added in the first step and further one liter of water is added in the second step. That is, Bills ('929) never uses a water-insoluble organic solvent that is an aliphatic hydrocarbon, aromatic hydrocarbon, halogenated hydrocarbon or a mixture thereof. Furthermore Bills ('929) discloses neither supplying a trace amount of water to water-insoluble organic solvent wherein the trace amount of water supplied is within such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent and water, nor precipitating ergosterol by a cooling crystallization from said solution thereof in a water-insoluble organic solvent containing the ergosterol.

Therefore the present invention cannot be achieved by any combination of Nimberger with Bills ('929).

On the other hand, Bills ('548) purified crude ergosterol prepared in Bills ('929) by precipitating by employing a mixture of acetone and ether as a solvent. That is, it uses neither hydrocarbon nor water.

And Bills ('548) discloses neither supplying a trace amount of water, wherein the trace amount of water supplied is within such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent and water, into the water insoluble organic solvent which is aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons

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completely different from the present invention, i.e., a method of separating ergosterol, wherein precipitating ergosterol by a cooling crystallization from said solution thereof in a water-insoluble organic solvent containing the ergosterol.

On the other hand, as discussed above in regard to the rejection in Office action paragraph no. 4, Bills ('929) discloses a process of preparing ergosterol by processing fungus fat extracted from fungi, by using suitable solvents, of which acetone is one (column 1, lines 37 to 40).

In the first step of Bills ('929), to 100cc. of fungus fat is added 500cc. of acetone, this solution is then mixed with a solution of caustic alkali, preferably potassium hydroxide, previously prepared by dissolving 25 grams of the alkali in 200cc. of 95 percent ethyl alcohol, the solution is then boiled gently for five to ten minutes to saponify it, and then allowed to be cooled (column 1, line 41 to column 2, line 54).

In the second step of Bills ('929), one liter of water is added to the saponification mixture, and the resultant solution chilled to about twenty degrees below zero centigrade so that all the ergosterol is precipitated as an amorphous mass, then the precipitate is removed from the soapy liquid by filtration or by centrifugal separation (column 2, lines 65 to 78).

That is, Knol discloses decomposing a sterol-zinc chloride addition product with water into zinc chloride and sterol. On the contrary, Bills discloses to add water to the saponification mixture, thereby to separate ergosterol. Accordingly, although both processes use water, both processes are completely different from each other.

Consequently Bills cannot be combined with Knol.

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On the other hand, an amount of water of Bills is one liter of water against 500cc. of acetone and 200cc. of ethyl alcohol (the acetone and ethyl alcohol may be further reduced for 5 to 10 minutes boiling). In addition, the acetone and ethyl alcohol are water-soluble solvents and they are not hydrocarbons, are required by claim 1.

Accordingly Bills ('548) discloses neither supplying a trace amount of water, wherein the trace amount of water supplied is within such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent and water, into the water-insoluble organic solvent, which is aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons or a mixture thereof, nor precipitating ergosterol by a cooling crystallization from said solution thereof in a water-insoluble organic solvent containing the ergosterol.

Thus neither Knol nor Bills discloses or suggests a method of separating ergosterol from a solution containing ergosterol in water-insoluble organic solvent that comprises supplying a trace amount of water to said solution and precipitating ergosterol by a cooling crystallization from said solution thereof in a water-insoluble organic solvent, when separating ergosterol from a water-insoluble organic solvent containing ergosterol.

Claim 5 remains rejected under 35 U.S.C. §103(a) as being unpatentable over Knol (*supra*) and Bills (*supra*), in view of Nimberger et al., (US 5,498,138). (Office action p.7)

Reconsideration of the rejection is respectfully requested in view of the amendment to claim 1.

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As discussed above, since the method of precipitating ergosterol of Knol is completely different from that of Bills, Bills cannot be combined with Knol.

In addition, neither Knol nor Bills discloses separating ergosterol from a solution containing ergosterol in water-insoluble organic solvent, which comprises supplying a trace amount of water to said solution and precipitating ergosterol by a cooling crystallization from said solution thereof in a water-insoluble organic solvent.

Accordingly there cannot be found any description or suggestion in any of the cited references to motivate applying Nimberger to Knol or Bills.

Consequently the present invention is not obvious over Knol, Bills and Nimberger, taken separately or in combination.

Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Knol (*supra*) and Bills (*supra*) as applied to claims 1, 3 and 6-8 above, in view of Watannabe et al., (US 4,447,362). (Office action p.8)

Reconsideration of the rejection is respectfully requested in view of the amendment to claim 1.

Watanabe teaches the process for the production of coenzyme Q from tissues of animals and plants or microbial cells which contain coenzyme Q, comprising treating with an alkali and saponifying, and extracting the treated suspension with at least one water-immiscible organic solvent.

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However, coenzyme Q is not a sterol such as ergosterol.

Each object to be extracted has a proper solvent. And a proper solvent for extraction is not necessarily a proper solvent for precipitation. In general, extracting solvent dissolves the object and precipitation solvent does not dissolve the object, i.e., the properties of such solvents are generally completely different from each other. Accordingly, it is not obvious to a person having an ordinary skill in this field to select a solvent suitable for extracting coenzyme Q as a proper solvent for precipitating ergosterol.

In addition, as mentioned above, Knol not Bills disclose neither a method of separating ergosterol from a solution containing ergosterol in water-insoluble organic solvent, wherein the water insoluble organic solvent is aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons or a mixture thereof, nor supplying a trace amount of water to said solution and precipitating ergosterol, wherein the trace amount of water supplied is within such a range of amount that no phase separation to form two liquid phases occurs between the water-insoluble organic solvent and water. Therefore amended claim 1 is not obvious over Knol and Bills.

Furthermore Watanabe does not disclose separating ergosterol from a solution containing ergosterol in water-insoluble organic solvent.

Therefore claim 4 is not obvious over Knol, Bills and Watanabe, taken separately or in combination.

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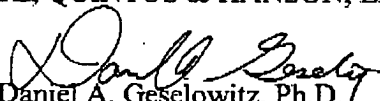
Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and intervening claims. (Office action p. 9).

Reconsideration of the objection is respectfully requested in view of the above arguments regarding base claim 1.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact the applicant's undersigned agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, the applicant respectfully petitions for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,
KRATZ, QUINTOS & HANSON, LLP


Daniel A. Geselowitz, Ph.D.
Agent for Applicant
Reg. No. 42,573

DAG/xl

Atty. Docket No. 090338
Suite 400
1420 K Street, N.W.
Washington, D.C. 20005
(202) 659-2930



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Enclosures: Petition for Extension of Time
IUPAC-NIST Solubility Database, Version 1.0 NIST Standard of Reference Database
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Solubility System: Hexane with Water

Components:

- (1) Water; H₂O; [7732-18-5] [NIST Chemistry WebBook](#) for detail
 (2) Hexane; C₆H₁₄; [110-54-3] [NIST Chemistry WebBook](#) for detail

Original Measurements:

Tsonopoulos, C.; Wilson, G.M., A. I. Ch. E. J. 1983, 29, 990-9.

Variables:

Temperature = 311-473 K

Pressure = 311-473 K

Prepared By:

G.T. Hefter

Experimental Remarks:

The three phase critical point was reported to be 496.7 K, 5.295 Mpa and $x_1 = 4.982$ (0.239 g(1)/100 g sln, compiler).

The authors also report equations fitted to their own and literature data over the range 273-497 K, viz.

$$\ln x_1 = -367.9847 + 16128.646/T + 52.820813 \ln T$$

$$\ln x_2 = -45.1714 - 1635.73/T + 7.53503 \ln T$$

Experimental Data: (Notes on the Nomenclature)

The solubility of hexane in water

T/K	Pressure [MPa]	10 ² * g ₁ /100 g solution (compiler)	10 ⁴ * Mole Fraction x_1
310.93	^a	0.114	0.238
366.48	^a	0.274	0.573
367.55	^a	0.256	0.535
373.15	0.3482	0.297	0.621
422.04	^a	1.30	2.71
423.15	1.2548	1.62	3.39
473.15	3.516	8.85	18.5

The solubility of water in hexane

T/K	Pressure [MPa]	g ₂ /100 g solution (compiler)	10 ² * Mole Fraction x_2
313.15	0.04537	0.025 (b)	0.117, 0.123
367.55	^a	0.124	0.595
373.15	0.3482	0.148	0.709
423.15	1.2548	0.667	3.11
473.15	3.516	2.52	11.0

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Notes:Table 1 ^a Not specified.Table 1 ^b Average value.**Method/Apparatus/Procedure:**

All experimental details are given in an Appendix deposited in a Documentation Centre rather than in the original paper. The solubility of (1) in (2) was measured by gas chromatography, whilst that of (2) in (1) was measured by Karl Fischer titration.

Source and Purity of Materials:

(1) Not details given.

(2) No details given.

Estimated Errors:Solubility: $\pm 5\%$ relative; repeatability of replicate analyses.

Temperature: not stated.

Pressure: $\pm 1\%$; type of error not stated.

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Black, C.; Joris, G.G.; Taylor, H.S., J. Chem. Phys. 1948, 16, 537-43.

Variables:

Temperature = 10-25 °C

Prepared By:

M.C. Haulait-Pirson

Experimental Data: (Notes on the Nomenclature)

Solubility of water in heptane at a total saturation pressure of 1 atm

t/°C	g/100 g solution	g/100 g solution (compiler)	10 ⁴ * Mole Fraction x ₂ (compiler)
10	0.0077	0.0077	4.28
20	0.0136	0.0136	7.56
20	0.0126	0.0126	7.00
25	0.0151	0.0151	8.39

Method/Apparatus/Procedure:

The method described in ref 1 in which tritium oxide acts as a tracer, was used.

Air saturated with radioactive water vapor was bubbled through the (1) sample until saturation was attained. Dissolved water was separated from (1) by absorption on calcium oxide. The tritium was transferred in the counter through equilibration with ethanol vapor.

Source and Purity of Materials:

(1) Ohio State University under an American Petroleum Institute project; purity not specified; used as received.

(2) not specified.

Estimated Errors:

Solubility: a few percent (type of error not specified).

References:¹Joris, G.G.; Taylor, H.S. J. Chem. Phys. 1948, 16, 45.

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Solubility System: Toluene with Water

Components:

- (1) Water; H₂O; [7732-18-5] [NIST Chemistry WebBook](#) for detail
 (2) Toluene; C₇H₈; [108-88-3] [NIST Chemistry WebBook](#) for detail

Original Measurements:

Polak, J.; Lu, B.C.Y., Can. J. Chem. 1973, 51, 4018-23.

Variables:

Temperature = 0-25 °C

Prepared By:

A. Maczynski and Z. Maczynska

Experimental Data: (Notes on the Nomenclature)

Solubility of toluene in water

t/°C	10 ³ * g ₁ /kg	g ₁ /100 g solution (compiler)	10 ⁴ * Mole Fraction x ₁ (compiler)
0(a)	724(c)	0.0724	1.42
25 (b)	573(c)	0.0573	1.12

Solubility of water in toluene

t/ °C	10 ³ * g ₂ /kg	g ₂ /kg Note	g ₂ /100 g solution (compiler)	10 ³ * Mole Fraction x ₂ (compiler)
0(a)	228	d	0.0228	1.17
25 (b)	543	c	0.0543	2.77

Notes:

Table 1 ^{a-c} see "ESTIMATED ERROR"

Method/Apparatus/Procedure:

Approximately 50 mL of 910 together with (2) were placed in a 125 mL Hypo-vial which was closed with a teflon coated rubber septum and placed in a constant-temperature water bath. The system was stirred magnetically for 24 hr and left in the bath for 3 days or was kept in the bath without stirring for 7 days, before samples were taken for analysis.

The solubility of water in the organic layer was determined by Karl Fischer titration and the solubility of hydrocarbon in the water layer was determined by gas chromatography.

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(1) matheson, Coleman and Bell, spectroquality grade reagent;
shaken three times with distilled water.

(2) distilled.

Estimated Errors:

Solubility: c) $\pm 1.7\%$; d) $\pm 4.7\%$; e) $\pm 3.1\%$ (mean)

Temperature: a) ± 0.02 K; b) ± 0.01 K

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